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ANGIOTENSIN-II, THE BRAIN, AND HYPERTENSION: AN UPDATE

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Despite enormous therapeutic advancements, the incidence of hypertension continues to rise [1] and remains a medical burden of global proportions [2]. This is likely due, in part, to the complex etiology of hypertension [1]. In addition to pathological processes in peripheral cardiovascular organs, the central nervous system (CNS) has emerged as a major culprit. The renin-angiotensin system (RAS) plays a crucial role in cardiovascular control, and both systemic Angiotensin-II (Ang-II) and centrally generated Ang-II signal through complex neural networks to contribute to the development of hypertension (Figure 1). While the effects of Ang-II within the brain are multifaceted, several key hypertensive players have emerged, including oxidative stress, endoplasmic reticulum stress, inflammation, and transcription factor activation. The purpose of this review is to provide a brief update on recent work related to Ang-II, the brain, and hypertension with a specific focus on *Hypertension* articles when appropriate.

Circulating Ang-II, centrally-generated Ang-II, and hypertension

Dysregulation of the RAS is common in human hypertension [3] and a number of hypertensive animal models have proven particularly useful to understand brain Ang-II, such as genetic, systemic infusion of Ang-II, deoxycorticosterone acetate (DOCA) dependent-salt and renal injury. Within the CNS Ang-II promotes a hypertensive state by enhancing sympathetic neural outflow, altering the release of hormones involved in volume, salt, vascular, renal and cardiac regulation, as well as modulating inflammatory processes. Emerging evidence also suggests that brain Ang-II may alter bone marrow derived hematopoetic stem and progenitor cells and thus exacerbate hypertensive vascular pathologies (Figure) [4-6]. Circulating Ang-II peptides are too large to cross the blood-brain-barrier (BBB) and act at circumventricular organs - specialized CNS regions lacking a well-formed BBB. These unique neural areas act as relay centers through which peripheral Ang-II can influence cardiovascular control via efferent projections to downstream autonomic/

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CONFLICT OF INTEREST / DISCLOSURES

None

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neurosecretory centers, including hypothalamic and brainstem regions [7]. However, BBB disruption is common in hypertension [8] and thus, provides a means by which circulating Ang-II could also gain access to neural regions from which it is typically excluded. In support of this, Biancardi et al. [9] recently employed novel intravascular fluorescent dyes and found increased BBB permeability in key cardioregulatory regions, including the paraventricular nucleus of the hypothalamus (PVN), nucleus tractus solitarii (nTS) and rostral ventral lateral medulla (RVLM), of spontaneously hypertensive rats (SHR), relative to normotensive controls. Administration of fluorescently labeled Ang-II also demonstrated that circulating Ang-II could gain access to neurons and glial cells within hypothalamic and brainstem regions of hypertensive animals. Interestingly, chronic treatment with the angiotensin type 1 receptor (AT_1R) antagonist losartan, but not a peripheral vasodilator, prevented the BBB disruptions. These findings raise the possibility that, in addition to acting at circumventricular regions, circulating Ang-II initiates a positive feedback loop through AT_1R to enhance BBB permeability and subsequently is able to access BBB-protected cardioregulatory neural areas.

In addition to circulating Ang-II, all components of the RAS system are present within the CNS and local production of brain Ang-II is now well accepted to contribute to hypertension development. The mechanisms by which the CNS generates Ang-II are reviewed in detail elsewhere [10]. Of importance, a key question has focused on how local production of Ang-II can occur when levels of renin, the rate-limiting enzyme, are extremely low. Attention has been drawn to the (pro)renin receptor, a transmembrane receptor that binds renin and its precursor prorenin at nanomolar concentrations. Thus, the (pro)renin receptor could facilitate extra- and intracellular Ang-II production, most likely through non-proteolytic activation of prorenin [11, 12]. In support of this, the (pro)renin receptor is widely expressed in neural cardioregulatory regions [13, 14] and is significantly upregulated in the brain of hypertensive animals [13]. More recently, Feng and colleagues [15] demonstrated in renin-angiotensinogen double-transgenic hypertensive mice that selective knockdown of the (pro)renin receptor in the subfornical organ (SFO), a circumventricular organ crucial for cardiovascular regulation, blunted hypertension and cardiac/vasomotor sympathetic tone, improved baroreflex sensitivity and reduced vasopression levels. Using DOCA-salt, a model that induces elevations in brain RAS activity and Ang-II signaling, the same group has also shown that neuron specific knockout of the (pro)renin receptor attenuates DOCA-salt-induced hypertension and sympathetic activation, concomitant with a reduction in brain Ang-II production [11]. Furthermore, a recently developed (pro)renin antagonist has been shown to attenuate DOCA-salt mediated increases in blood pressure and brain Ang-II, highlighting the therapeutic potential in targeting brain pro(renin)-mediated Ang-II production in hypertensive conditions [16].

Whether centrally- or peripherally-generated, the hypertensive actions of brain Ang-II occur primarily via AT_1R. Indeed, Cre-LoxP-mediated removal of AT_1R from catecholaminergic cells blunts Ang-II-dependent hypertension and sympathetic modulation of blood pressure [17]. These data suggest that AT_1R in this cell population, presumably within sympathetic premotor neurons, the adrenal medulla and sympathetic ganglia, are involved in the hypertensive actions of Ang-II, although a role for AT_1R in peripheral cell populations, such as T lymphocytes, cannot be excluded from these findings. Additional support for brain

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AT_1R signaling has also been demonstrated in a murine DOCA-salt model. Hilzendeger et al. [18]showed that selective knockdown of AT_1R in the SFO blunted elevations in arterial blood pressure, reduced sympathetic cardiac modulation and urine vasopression markers (copeptin), and positively affected fluid and salt homeostasis. Collectively, these recent findings build upon existing evidence and provide additional insight into specific CNS nuclei and cell populations involved in the development of hypertension due to brain Ang-II-AT_1R signaling.

While the primary actions of AT_1R are prohypertensive, as highlighted by the aforementioned studies, it is important to consider the neural region in which Ang-II-induced signaling occurs. The nTS, located in the dorsomedial aspect of the brainstem, is a key example. Stimulation of excitatory nTS projections activate inhibitory neurons in the caudal ventrolateral medulla, in turn inhibiting sympathoexcitatory neurons in the RVLM, resulting in decreases in arterial blood pressure. Indeed, recent observations indicate that AT_1R expression is elevated in the nTS of SHR and small-hairpin RNA knockdown of AT_1R in the nTS of hypertensive animals resulted in an approximate 30 mmHg increase in mean arterial pressure [19]. These findings suggest that nTS Ang-II-AT_1R-signaling exerts counter-hypertensive actions. While outside of the context of this brief review, the compensatory actions of AT_2R [20] and alternative RAS pathways (ACE2/Ang-1-7/Mas) [21] should also be considered.

Ang-II, brain oxidative stress, and hypertension

Over the past 20 years, a wealth of evidence has emerged implicating Ang-II-induced reactive oxygen species (ROS) generation in the pathogenesis of hypertension. Although a number of sources for ROS exist, NAD(P)H (nicotinamide adenine dinucleotide phosphate) oxidase is currently viewed as the predominant source of Ang-II-derived ROS production in the brain [22]. A number of recent reports extend our understanding of ROS in the CNS in mediating the hypertensive actions of Ang-II. Building upon previous findings demonstrating an obligatory role for ROS in the SFO in mediating Ang-II-dependent hypertension [23-25], Lob et al. [26] used a Cre-LoxP approach to ablate the NAD(P)H oxidase docking subunit p22(phox) from the SFO in a murine model. In response to low dose infusion of Ang-II, removal of SFO p22(phox) prevented ROS production in the SFO and eliminated the hypertensive response; further demonstrating that NAD(P)H oxidase derived ROS in the CNS promote Ang-II-dependent hypertension [24, 25, 27]. In line with these findings, overexpression of the (pro)renin receptor in neuronal cultures and elevations in Ang-II production promotes an increase in ROS that is dependent upon NAD(P)H oxidase activity, although Ang-II independent mechanisms also contribute [28].

Parallel investigations have focused on additional mechanisms mediating Ang-II-induced oxidant production in the CNS. Cycylooxygenase (COX)-derived prostanoids have been implicated in the development of hypertension, although the source and site of action remain incompletely defined. In this regard, we recently demonstrated crosstalk between brain prostaglandin E_2, its receptor EP_1 and ROS signaling in the development of Ang-II-induced hypertension. In response to systemic Ang-II infusion, hypertension and SFO-ROS production were abolished in mice with null mutations in the EP_1 receptor and

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cyclooxygenase-1 [COX-1; the enzymatic source of prostaglandin E_2], but not COX-2 [29]. Genetic reconstitution of the EP_1 receptor selectively in the SFO was sufficient to restore these responses, demonstrating that COX-1 derived prostaglandin E_2 ROS generation in the forebrain SFO is required for Ang-II-dependent hypertension [29]. Consistent with this, treatment with a selective COX-1 inhibitor (but not COX-2 inhibitor) has been shown to attenuate hypertension development and increases in whole body norepinephrine spillover in response to Ang-II infusion in rats on a high salt diet [30]. At the cellular level, recent in vitro findings in SFO cells suggests a complex signaling cascade in which Ang-II, via AT_1R, promotes phospholipase A_2-induced production of arachidonic acid [31]. Arachidonic acid is then metabolized to prostaglandin E_2 by COX-1 and acts upon the EP_1 receptor (most likely in a paracrine fashion) to cause intracellular Ca^{2+} release. Subsequent elevations in intracellular Ca^{2+} promote NAD(P)H oxidase derived ROS production and activation of voltage-gated Ca^{2+} channels, resulting in increases in neuronal firing [31]. Together, these recent findings, from the cellular to whole animal level, provide in depth insight into the mechanisms by which brain Ang-II-induced oxidative stress promotes hypertension development.

Ang-II, brain endoplasmic reticulum stress, and hypertension

The endoplasmic reticulum (ER) is a reticulated organelle specialized in the synthesis, folding, assembly and modification of proteins. The ER also plays an important role in various cellular signaling processes and ER homeostasis is strictly maintained in the face of a broad spectrum of potential stressors. However, prolonged periods of cell stress, such as those induced by Ang-II (e.g., alterations in cellular redox status and Ca^{2+} levels), can lead to an accumulation of un/misfolded proteins in the ER, triggering an adaptive signaling cascade, the unfolded protein response (UPR). While initially a compensatory attempt to maintain cellular homeostasis, sustained activation of the UPR is now thought to be the basis of a number of chronic diseases [32]. In this regard, we have recently shown that brain ER stress mediates the development of Ang-II-dependent hypertension [33]. In response to low dose Ang-II infusion, robust UPR upregulation and ER morphological alterations were found in the CNS, particularly within the SFO. CNS delivery of a chemical ER stress inhibitor (tauroursodeoxycholic acid) or genetic inhibition of ER stress selectively in the SFO abolished the development of Ang-II-induced hypertension. Interestingly, inhibition of SFO-ER stress also prevented Ang-II-mediated elevations in ROS, suggesting that Ang-II-induced ER stress is a source of oxidative stress [33].

In line with these findings, Chao et al. [34] found upregulation of the UPR in the RVLM of SHR, or in response to intracisternal infusion (which globally targets medullary regions) of Ang-II in control animals. Intracisternal infusion of salubrinal, a pharmacological agent that reduces ER stress, resulted in a reduction in arterial blood pressure in SHR. Interestingly, RVLM-targeted administration of the ROS scavenger tempol lessened Ang-II- and SHR-induced UPR activation, suggesting that ROS may also act upstream of ER stress [34]. A number of recent observations have also suggested a role for ER stress in mediating cardiac damage, endothelial dysfunction and aortic stiffening during Ang-II-induced hypertension [35, 36]. It is important to note that although these investigations were not focused on the CNS, the results are based around systemic administration of ER stress

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reducing agents that will act not only peripheral regions, but also within the brain, particularly at blood-brain-barrier deficient regions (e.g., SFO). Although yet to be determined, given the importance of the CNS in these pathological processes [37], a role for brain ER stress cannot be excluded. Collectively, these findings highlight Ang-II-induced ER stress in the brain as a novel paradigm underlying the development of hypertension. [38] However, it is important to consider the model of hypertension that is investigated, as Jo et al. [39] recently reported that relief of brain ER stress (with chemical chaperones) attenuated DOCA-salt-induced elevations in saline intake and heart rate, with no influence on the pressor response. Thus, it is plausible that brain ER stress may play a role in certain forms of hypertension (e.g. systemic Ang-II and genetic models), but not others (e.g. DOCA-salt dependent). This possibility will require further comparative investigation in various models of hypertension.

Ang-II, brain inflammation, and hypertension

In addition to modulation of the autonomic nervous system and volume homeostasis, the CNS actions of Ang-II promote activation of the immune system. This area of research is particularly intriguing, given the emerging role of the immune system and inflammation in the pathogenesis of hypertension [40, 41]. During low dose infusion of Ang-II in mice, lesioning of the anteroventral third cerebral ventricle region concomitantly prevents peripheral vascular infiltration of activated T cells and hypertension development [42] - supporting the concept of brain Ang-II signaling in the regulation of peripheral inflammation. A key link between CNS Ang-II and immune system activation appears to be oxidative stress, particularly within the SFO. Indeed, selective SFO removal of extracellular superoxide dismutase, to induce elevations in ROS, resulted in exaggerated elevations in circulating activated T cells and vascular infiltration of inflammatory cells during Ang-II-induced hypertension [43]. In line with this, ablation of the NAD(P)H oxidase subunit p22(phox) from the SFO prevents Ang-II-induced inflammatory responses in the peripheral vasculature [26].

While the precise mechanisms by which brain Ang-II impacts the peripheral immune system remain incompletely defined, as detailed elsewhere [40, 41, 44-46], enhanced sympathetic outflow or removal of suppressive parasympathetic influence to lymphoid organs, direct adrenergic and cholinergic modulation of immune cell populations, or hypertension itself may all contribute. Building upon previous observations of elevations in splenic sympathetic nerve activity and inflammatory cytokine expression in response to central Ang-II administration [47], a series of recent experiments from Raizada's group indicates a link between CNS Ang-II, sympathetic input to bone marrow, and inflammatory responses. Central scavenging of mitochondrial ROS, with a superoxide dismutase mimetic, prevented Ang-II-induced increases and decreases in circulating bone marrow derived inflammatory and endothelial progenitor cells (vascular reparative cells crucial for repair and maintenance of the endothelium), respectively. In addition, retrograde neuronal labeling demonstrated a brain to bone marrow connection, with efferent inputs arising from a number of cardioregulatory regions including the PVN, RVLM, nTS, and SFO [6]. More recently, parallel elevations in sympathetic nerve activity to bone and an imbalance in inflammatory and endothelial progenitor cells was found in SHR, compared to normotensive control rats [5],

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although the role of Ang-II in these processes remains yet unknown. Collectively, these novel findings suggest that Ang-II-mediated increases in ROS within the CNS may contribute, in part, to peripheral inflammatory responses, while at the same time inhibiting vascular reparative processes, through efferent signaling to bone marrow.

It is important to consider that along with a CNS-immune system connection, immune system-CNS communication also plays a role in Ang-II-induced hypertension. For example, acute injection of the pro-inflammatory cytokine TNFα into the PVN induces elevations in arterial blood pressure, as well as lumbar and splanchic sympathetic nerve activity [48]. Furthermore, chronic infusion of Ang-II promotes microglia activation and proinflammatory cytokine production in the PVN; responses that are prevented with central administration of an anti-inflammatory antibiotic, PVN-selective overexpression of the anti-inflammatory cytokine interleukin-10, or scavenging of mitochondrial ROS [6, 49]. Interestingly, inhibition of central Ang-II induced inflammatory responses have also been shown to correct the imbalance in circulating inflammatory and endothelial progenitor cells [6]. In addition to inflammatory activation within cardioregulatory nuclei, Paton and colleagues have theorized that activation of AT_1R on cerebrovascular endothelial cells may promote vascular inflammation in the brainstem, thus contributing to the development of hypertension through altered vascular-neuronal signaling [50]. While the precise interplay remains unclear, the overall evidence to date suggests that a positive feedback loop likely exists in which Ang-II promotes inflammatory cascades with the brain, which subsequently promote activation of the peripheral immune system. In turn, activated circulating inflammatory cells may then feedback to the brain further perpetuating the process. In support of this, proinflammatory bone marrow derived cells have been shown to migrate into the PVN of SHR [51], whereas Ang-II-induced hypertension is associated with T-cell infiltration in the SFO [52]. In addition, recent intriguing findings indicate that acute microinjection of proinflammatory cytokines (TNF- α and IL-1β) into the SFO induced elevations in renal sympathetic nerve activity and arterial blood pressure – responses that were prevented by blocking the RAS or COX-2. Moreover, SFO-targeted proinflammatory cytokine microinjections were associated with increases in RAS and COX-2 activity in the SFO and PVN, suggesting that brain inflammation may facilitate the hypertensive actions of brain Ang-II [53].

Ang-II, brain transcription factors, and hypertension

In order for CNS Ang-II-signaling to cause sustained elevations in arterial blood pressure, transcription of genes that alter neuronal structural and functional properties is necessary [54]. The inducible transcription factors nuclear factor κB (NFκB) and activator protein 1 (AP-1) have been shown to be strongly associated with ROS, ER stress and inflammatory responses. While in vitro examinations have clearly shown a role for these two transcription factors in neuronal signaling [54], translation of these findings to the in vivo hypertension setting has been limited.

Following 2-week [55] or 4-week [56] systemic infusion of Ang-II in rats, upregulation of NFκB subunits, as well as increased activity of the p65 subunit, was found in the PVN; responses that were prevented by CNS antagonism of AT_1R or scavenging of superoxide with intracerebroventricular administration of losartan or tempol, respectively [56].

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Pharmacological [56] and PVN-targeted genetic inhibition of NFκB [55] attenuated the development of Ang-II-induced hypertension, suggesting a functional role for this transcription factor, although further studies are warranted to determine the extent of NFκB activation in the PVN *prior* to the development of hypertension. In this context, we recently used the novel technique of in vivo bioluminescence imaging to track temporal activation of NFκB in the brain during the development of hypertension [57]. In brief, this technique capitalizes upon luciferase-dependent light emission and allows for in vivo determination of transcription factor activation in the same mouse over time [58, 59]. Utilizing this approach an AT_{1a}R-, ROS-, and ER-stress mediated prehypertensive surge in NFκB activation was found in the SFO during the development of Ang-II-induced hypertension [57]. While yet to be completely understood, collectively these data indicate that a complex NFκB neural network is involved in Ang-II-mediated hypertensive actions, with initial activation occurring in circumventricular organs that are subsequently followed by downstream activation in other cardioregulatory regions.

In addition to NFκB, Burmeister et al. [58] examined a role for the transcription factor AP-1 in the PVN in a murine 2-kidney-1-clip model of hypertension, which is associated with activation of the brain RAS [60]. Temporal in vivo bioluminescence imaging evaluation revealed a progressive redox-dependent rise in PVN AP-1 activity that surged within 5 days and remained elevated for up to two weeks after renal artery clipping, whereas dominant-negative inhibition of AP-1 transcriptional activation in the PVN prevented renovascular hypertension. Collectively, these studies highlight the importance of CNS transcription factor activation in models of hypertension dependent upon brain Ang-II, although future studies are needed to dissect out additional neural regions and pathways involved.

Summary: Ang-II, the brain, and hypertension

Great strides have been made in recent years to advance our understanding of Ang-II actions in the brain in mediating neurogenic hypertension. It is now evident that peripherally- and locally-generated Ang-II promote a hypertensive state through influences on redox, ER, inflammatory, and transcription factor pathways in the brain (Figure). However, an integrated and complete understanding of these pathological processes is still lacking. Moving forward, novel approaches and techniques will be necessary to further our understanding of Ang-II, the brain and hypertension, such as intricate neural network analyses, temporal evaluations of signaling pathways, and integration of CNS molecular processes with physiological endpoints. Moreover, while much has been learned from experimental animal models of hypertension, we must continue to ask whether Ang-II-mediated brain mechanisms act in the same manner in human hypertension.

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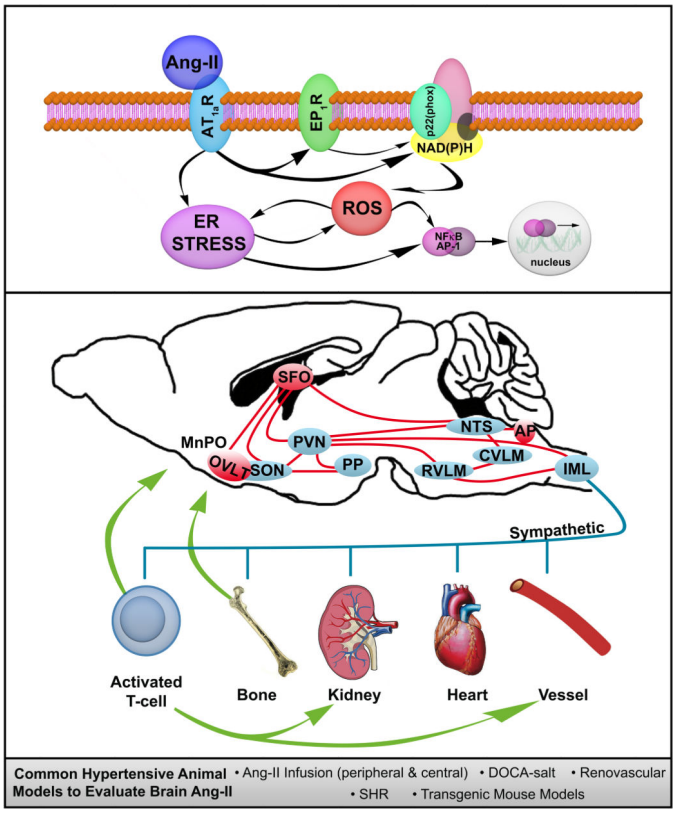

FIGURE.

Simplified schematic illustrating the signaling pathways (top box), as well as neural networks and sympathetic nervous system influenced physiological outputs (middle box) involved in the development of hypertension due to peripherally- or locally-generated Angiotensin-II (Ang-II) action in the brain. Common animal models used to evaluate Ang-II, the brain and hypertension are also highlighted (bottom box). See text for additional details. AP, area postrema; AP-1, activator protein-1; $AT_{1a}R$, Angiotensin type 1a receptor; CVLM, caudal ventral lateral medulla; DOCA, deoxycorticosterone acetate; ER, endoplasmic reticulum; EP_1R, prostaglandin E receptor 1; IML; intermediolateral nucleus; MnPO, median preoptic nucleus; NAD(P)H, nicotinamide adenine dinucleotide phosphate; NTS, nucleus tractus solitarii; NFκB, nuclear factor κB; OVLT, organum vasculosum lamina terminalis; PP, posterior pituitary; PVN, paraventricular nucleus of the hypothalamus; ROS, reactive oxygen species; RVLM, rostral ventral lateral medulla; SHR, spontaneously hypertensive rat; SFO, subfornical organ; SON, supraoptic nucleus.